PATENT
Attorney Docket No. 06478.1495-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Peter Hermentin et al.	Group Art Unit: 1641
Application No.: 10/682,199	Examiner: Venci, David J.
Filed: October 10, 2003	
For: METHOD FOR DETERMINING MULTIMERS OF PLASMA PROTEINS	Confirmation No.: 1253

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Pursuant to 37 C.F.R. § 41.41, Appellants present this Reply to the Examiner's Answer dated November 19, 2007.

I. STATUS OF THE REJECTIONS

In response to the Appeal Brief filed August 10, 2007, the following rejections remain:

1. Claims 16-24, 27-28, 30-31, 33, and 35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Shainoff*, "Electrophoresis and direct immunoprobing on glyoxal agarose and polyacrylamide composites," Advances in Electrophoresis, 6: 65-176 (1993).
2. Claims 16-24, 27-28, 30-31, 33, and 35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable in view of *Bhat* & *Nagineni*, "Use of

submarine gel electrophoresis for running multiple two-dimensional protein gels," Analytical Biochemistry, 170: 105-109 (1988).

3. Claim 25 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over *Shainoff* and *Bhat & Nagineni*, and further in view of *Perrella & Denisov*, "Low temperature electrophoresis methods," Methods in Enzymology, 259: 468-487 (1995).

II. ARGUMENT

Appellants have considered the Examiner's Answer and, in view of it, have the following remarks.

A. *SHAINOFF* DOES NOT TEACH USING ALL OF THE ELEMENTS ALLEGED BY THE EXAMINER

In rejecting claims 16-24, 27-28, 30-31, 33 and 35 as obvious under 35 U.S.C. § 103(a), the Examiner relies primarily on *Shainoff*, "Electrophoresis and direct immunoprobing on glyoxal agarose and polyacrylamide composites," Advances in Electrophoresis, 6: 65-176 (1993). The Examiner also relies upon *Bhat & Nagineni*, "Use of submarine gel electrophoresis for running multiple two-dimensional protein gels," Analytical Biochemistry, 170: 105-109 (1988). Appellants assert, however, that *Shainoff* does not teach using all of the elements alleged by the Examiner, instead *Shainoff* teaches away from certain elements.

Claims 16-24, 27-28, 30-31, 33 and 35 are drawn to a method for determination of multimers of multimer-forming proteins by gel electrophoresis. These claims recite, *inter alia*, three essential elements of the instantly claimed invention: (1) fractionating a sample containing von Willebrand factor or fibrinogen into multimer bands by submarine

electrophoresis in agarose gel wherein the agarose gel is continuous, homogeneous and free of lumps; (2) visualizing multimer bands by a dye in the gel; (3) quantifying the dyed multimer bands. The Examiner cites *Shainoff* for all the elements of claim 16 except for submarine gel electrophoresis. The Examiner cites *Bhat & Nagineni* for submarine gel electrophoresis, as will be discussed in detail below.

As discussed on page 8 of the Appeal Brief, *Shainoff* is a review article that describes a variety of procedures that use ***glyoxyl agarose***, which is an oxidized composite material formed from agarose and glycidol and polyacrylamide composites. The claims of the present invention, however, are directed to regular agarose. The Examiner has previously asserted that *Shainoff* teaches agarose gel electrophoresis (see Examiner's Answer, page 6); however, *Shainoff* only used regular agarose either (1) as a control for comparison to the glyoxyl agarose gels which were the focus of the article or (2) to make a composite gel by blending regular agarose with glyoxyl agarose for good gel strength and shelf life. (See *Shainoff*, pages 67, line 14 and 72, lines 5-6). These teachings do not suggest using regular agarose gels for resolving multimer proteins. It is essential that the record reflects that *Shainoff* teaches using glyoxyl agarose gels, instead of regular agarose gels. In fact, *Shainoff* teaches away from using regular agarose gels when it emphasizes the advantages of glyoxyl agarose in the very first paragraph of the review article:

> Glyoxyl agarose is **unique** among protein immobilizing media, the **only** such medium presently available that can be (i) melted into pre-derivatized form for casting into a requisite format for separations, and (ii) turned on and off repeatedly for sequential separating and fixing any substance possessing at least a single amino group.

Shainoff certainly has a bias for glyoxyl agarose gels, and therefore a bias against regular agarose gels, as used in the present invention.

Furthermore, the Examiner has not adequately addressed Appellants statements that immunostaining was preferred to dye staining. The Examiner indicates that there are no statements in *Shainoff* supporting Appellant's bias against dye staining; however, the Examiner apparently ignores Appellant's citation to the legend of Figure 4, which highlights the broad bands produced by immunostaining "because of the greater sensitivity and intensity of staining." Therefore, Appellants believe that *Shainoff* does, like the art in general, teach a bias for immunostaining, and thus a bias against dye staining.

In conclusion, Appellants assert that a balanced reading of *Shainoff* shows that this reference does not teach using dye stained, continuous agarose gels. *Shainoff*, instead, teaches away from using those elements, but instead teaches using composite gels and immunostaining.

B. DESPITE THE EXAMINER'S ALLEGATIONS, THERE IS NO REASON TO COMBINE THE GEL TEACHINGS OF *SHAINOFF* AND *BHAT & NAGINENI*

The Examiner has relied upon the combination of *Shainoff* and *Bhat & Nagineni* to reject the claims of the present invention. Appellants have argued, and continue to maintain, that there is no reason to combine *Shainoff* and *Bhat & Nagineni*. The Examiner relies upon *Bhat & Nagineni* for the teaching of submarine electrophoresis. However, as discussed in the Appeal Brief at pages 13-14, *Bhat & Nagineni* discusses 2D polyacrylamide gel electrophoresis, which by definition requires the use of two different gels, and is quite unlike the continuous one dimensional agarose gels used in

the present invention. Although *Bhat* and *Nagineni* successfully used submarine electrophoresis for 2D gels (which each require the use of two different gels), it does not provide any reason to believe this technique will be advantageous for one dimensional single gel electrophoresis, as taught in the claimed invention. Additionally, *Bhat* & *Nagineni* uses polyacrylamide gels, whereas the present invention uses agarose gels. Again, the Examiner has provided no reason to use the techniques of *Bhat* & *Nagineni* in the significantly different system of the present invention (or to combine them with the systems of *Shainoff*).

The Examiner does not address this argument in the Reply Brief, but only states that:

> One cannot show nonobviousness by attacking the teachings of *Shainoff* and *Bhat* & *Nagineni* individually where the rejections are based on the combinations of references.

(Reply Brief page 7). Appellants maintain that they are not attacking the references individually, but instead assert that there is no reason to combine these references, nor an expectation that the submarine technique would be beneficial in a substantially different electrophoretic system. In the Reply Brief, the Examiner has not substantively addressed the question of why the skilled artisan would have a reason to combine these references. Therefore, Applicants assert that this rejection cannot stand.

C. *PERRELLA & DENISOV* DOES NOT TEACH ALL OF THE ELEMENTS ALLEGED BY THE EXAMINER

As discussed in prior papers, the Examiner further relies on *Perrella* & *Denisov*, "Low temperature electrophoresis methods," Methods in Enzymology, 259: 468-487 (1995) in rejecting claim 25 as obvious under 35 U.S.C. § 103(a). Claim 25 further

recites that the gel electrophoresis is carried out at temperatures between 8°C and 12°C. The Examiner apparently relies upon *Perrella* & *Denisov* as teaching low temperature electrophoresis.

Perrella & *Denisov*, however, does not teach operating a gel electrophoresis at the claimed temperatures, nor does it suggest this range of temperatures, any temperatures within this range, or even any overlapping temperature ranges. Appellants pointed this out in the Appeal Brief. In reply, the Examiner merely indicated that:

> With respect to the precise temperature range of claim 25, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves routine skill in the art. See *In re Aller,* 105 USPQ 233 (CCPA 1955).

(Examiner's Reply Brief, at page 7). Appellants further study of the *Perrella* & *Denisov* reference confirms our earlier understanding that *Perrella* & *Denisov* teaches ***different*** temperatures and that the *Perrella* & *Denisov* temperatures do not overlap with the claimed range. Specifically, *Perrella* & *Denisov* teaches only temperatures that are below freezing:

- Cryogenic . . . electrophoresis (pages 469-470);
- -40° and -30° (page 470);
- narrow range of subzero temperatures >-10° (page 471);
- -10° (pages 471 and 472);
- -50°, -45°, and -25° (page 472);
- -25° (pages 473, 475, and 477 with incubation steps at different temperatures on page 475); and
- -30° (page 478).

Because all of the other units in *Perrella* & *Denisov* are in metric units, and because Celsius is the standard temperature scale used in scientific articles, Appellants assert

that it is reasonable for the Office to assume these temperatures are in Celsius. Additionally, Appellants assert that *Perrella & Denisov* actually teaches away from using temperatures above freezing, such as the claimed 8-12°C temperature range, especially since at the cryogenic temperatures of *Perrella & Denisov* require substantially different buffer composition so that the electrophoresis buffers will not freeze (ethylene glycol, methanol, dimethyl sulfoxide, and the like). Therefore, because *Perrella & Denisov* teach away from using temperatures above freezing, and because their cryogenic temperatures require unique gel conditions, claim 25 is not obvious over this combination of references.

III. CONCLUSION

As discussed in the Appeal Brief filed August 10, 2007, Appellants submit that the Examiner has failed to establish that one of ordinary skill in the art would have had "a good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727 (2007) (emphasis added). For at least these reasons, Appellants respectfully submit that the instantly claimed invention is not obvious in view of the cited combinations of prior art references.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 17, 2008

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